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Update on Paraneoplastic Neurologic Disorders

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the symptoms of paraneoplastic neurologic disorders (PNDs) and, when appropriate, include PNDs in the differential diagnosis when evaluating patients with systemic cancers.
2. Describe the relationship of paraneoplastic antibodies and specific syndromes, where present, and their use in diagnosis of PND.

ABSTRACT

When patients with cancer develop neurologic symptoms, common causes include metastasis, infections, coagulopathy, metabolic or nutritional disturbances, and neurotoxicity from treatments. A thorough clinical history, temporal association with cancer therapies, and results of ancillary tests usually reveal one of these mechanisms as the etiology. When no etiology is identified, the diagnosis considered is often that of a paraneoplastic neurologic disorder (PND). With the recognition that PNDs are more frequent than previously thought, the availability of diagnostic tests, and the fact that, for some PNDs, treatment helps, PNDs should no longer be considered diagnostic zebras, and when appropriate should be included in the differential diagnosis early in the evaluation. ***The Oncologist*** 2010;15:603–617

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Introduction

This article focuses on paraneoplastic neurologic disorders (PNDs) that are either known or strongly suspected to be immune mediated. In these PNDs, the main targets of the immune responses are neurons and peripheral nerves, although any part of the central, peripheral, or autonomic nervous system, including the retina and muscle, can be involved [1]. In some PNDs, one area of the brain or a subset of neurons is predominantly affected (e.g., Purkinje cells in paraneoplastic cerebellar dysfunction), whereas in others multiple regions of the nervous system can be affected (brain and spinal cord in encephalomyelitis). Therefore, PNDs encompass a wide spectrum of neurologic signs and symptoms that frequently mimic similar noncancer related neurologic disorders.

Immune Responses in PNDs

Although the exact pathogenesis of most PNDs is unclear, it is generally believed that expression of neuronal proteins by a cancer breaks immune tolerance to proteins normally expressed in the nervous system. In response, patients develop antineuronal antibodies that can be found in serum

Table 1. Antibodies that are markers of paraneoplastic neurologic syndromes

Antibody	Associated neurologic syndrome(s)	Tumors
Anti-Hu	Encephalomyelitis, subacute sensory neuronopathy	SCLC
Anti-Yo	Cerebellar degeneration	Ovary, breast
Anti-Ri	Cerebellar degeneration, opsoclonus	Breast, gynecologic
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
Anti-CV2/CRMP-5	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy	SCLC, thymoma, several
Anti-Ma proteins	Limbic, hypothalamic, brainstem encephalitis	Testicular (Ma2), several (Ma)
Anti-amphiphysin	Stiff-man syndrome, encephalomyelitis	Breast, SCLC
Anti-recoverin and others[a]	Cancer and melanoma-associated retinopathy	SCLC (CAR), melanoma (MAR)

[a]A variety of target antigens have been identified.
Abbreviations: CAR, cancer-associated retinopathy; CRMP, collapsing response-mediator protein; MAR, melanoma associated retinopathy; SCLC: small-cell lung cancer.

Table 2. Antibodies that can occur with and without cancer association

Antibody	Neurologic syndrome	Cancer type when associated
Anti-AChR (muscle)[a]	Myasthenia gravis	Thymoma
Anti-ACh (neuronal)[a]	Autonomic neuropathy	SCLC
Antibodies to proteins that associate with VGKCs[b]	Neuromyotonia, limbic encephalitis	Thymoma, SCLC
Anti-VGCC[c]	LEMS, cerebellar degeneration	SCLC
Anti-NMDAR[d]	Anti-NMDAR encephalitis	Teratoma
Anti-AMPAR[d]	Limbic encephalitis with relapses	SCLC, thymoma, breast
Anti-GABA(B)[d]	Limbic encephalitis, seizures	SCLC, neuroendocrine
Anti-GAD[d]	Stiff-person, cerebellar syndromes	Thymoma

[a]A direct pathogenic effect of these antibodies has been demonstrated.
[b]Antibodies to proteins that associate with VGKCs are proven to be pathogenic for neuromyotonia.
[c]Anti-VGCC antibodies are proven to be pathogenic for LEMS. They occur similarly in paraneoplastic and nonparaneoplastic LEMS. The pathogenic role of the antibodies for cerebellar degeneration is unclear; however, they are almost always associated with an underlying SCLC (e.g., patients with cerebellar degeneration and VGCC antibodies usually have SCLC).
[d]These antibodies are strongly suspected but have not yet been proven to be pathogenic.
Abbreviations: AChR, acetylcholine receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor; GABA(B), γ-amino-butyric acid type B; GAD, glutamic acid decarboxylase; LEMS, Lambert-Eaton myasthenic syndrome; NMDAR, N-methyl-D-aspartate receptor; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel.

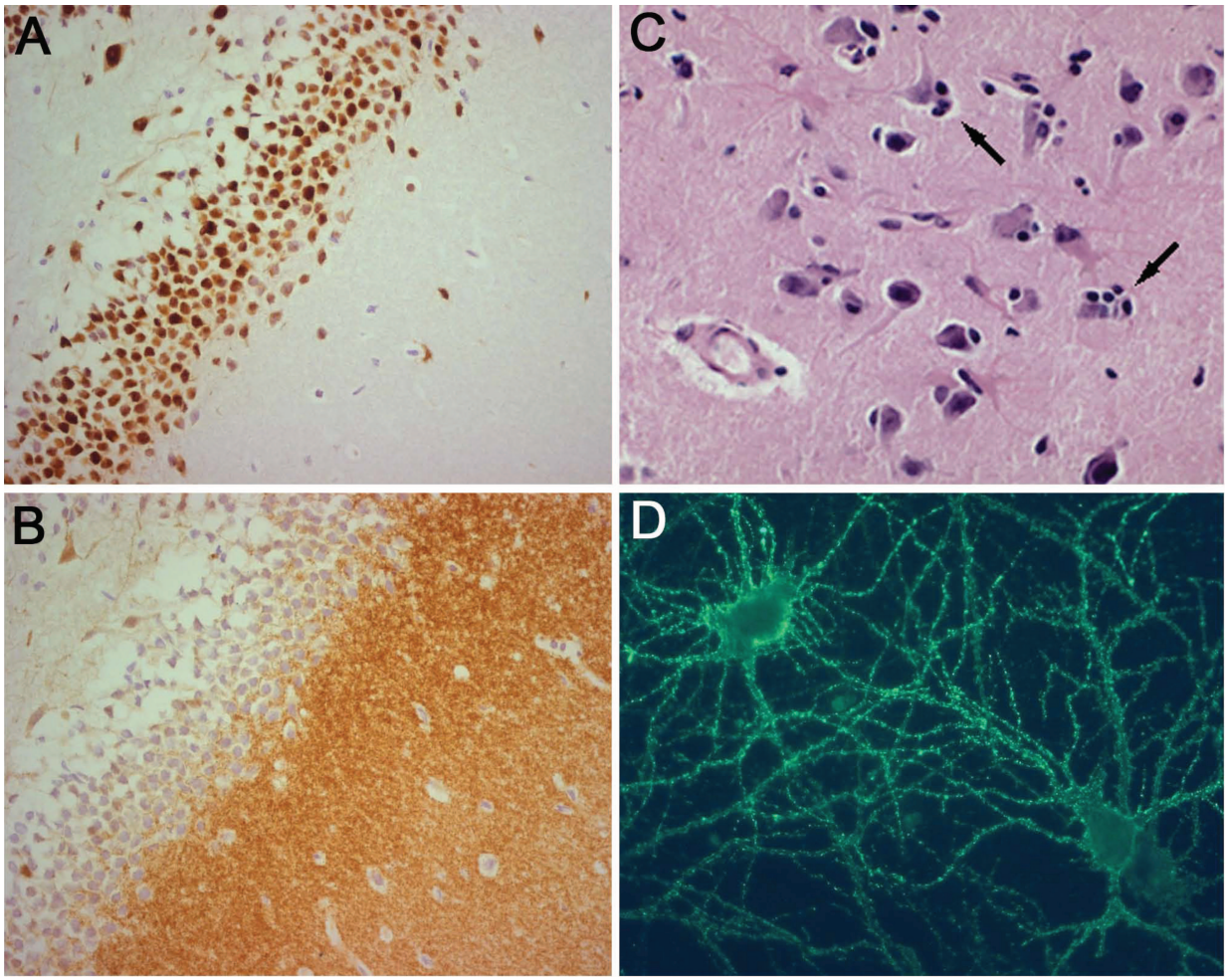

Figure 1. Antineuronal antibodies and brain T-cell infiltrates in paraneoplastic encephalitides. Consecutive sections of rat hippocampus immunolabeled with antibodies to intracellular (anti-Hu antibody) **(A)** and cell surface (anti-NMDA receptor antibody) **(B)** neuronal antigens. Note the distinct patterns of reactivity limited to neuronal cell bodies **(A)** and to neuronal processes present in the neuropil of the hippocampus **(B)**. A biopsy of the temporal lobe of a patient with limbic encephalitis and antibodies to intracellular antigens (anti-Ma2) shows predominant T-cell infiltrates surrounding and indenting neurons (arrows) **(C)**. Cultures of rat hippocampal neurons incubated with antibodies to cell surface antigens (AMPA receptor) show intense cell surface immunolabeling **(D)**.

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate.

and cerebrospinal fluid (CSF). When present, the antibodies serve as markers of the paraneoplastic origin of the neurologic symptoms (Table 1). A direct pathogenic role of the antibodies has, however, been proven in only a few PNDs (Table 2) [2–4]. In general, the antibodies that are likely pathogenic are directed against cell surface antigens (Fig. 1B, 1D). In these disorders, the antineuronal antibodies interfere with neuronal cell signaling or synaptic transmission. Evidence supporting an immune pathogenesis in the other PNDs includes responses to immunomodulatory therapies and in vitro studies demonstrating antineuronal effects of the antibodies [5–9]. In contrast, when antibodies are directed against intracellular antigens, the pathogenic mechanism appears to be mediated by cytotoxic T cells (Fig. 1A, 1C). In these cases, autopsies of patients with PNDs of the central nervous system (CNS) often demonstrate intense inflammatory infiltrates of mononuclear cells, including $CD4^+$ and $CD8^+$ cells, which predominate in the areas that are symptomatic [10–12]. The exact mechanism whereby cytotoxic T cells recognize antigens expressed in neurons that normally lack expression of the antigen-presenting major histocompatibility complex class I and II molecules is unknown, but in these disorders it is likely that T cells are the effectors of the neuronal damage [13].

Although the presence of paraneoplastic antibodies confirms the diagnosis of a PND, it is important to recognize that PNDs may occur without associated antibodies, and

that paraneoplastic antibodies are occasionally found at low titers in a variable proportion of patients with cancer without neurologic symptoms [14–16]. The presence of antibodies, therefore, should not be the only condition for defining a neurologic syndrome as paraneoplastic. Furthermore, there is a group of antibodies that associate with neurologic syndromes both in the presence and absence of cancer (Table 2) [17]. Experience suggests that finding high titers of paraneoplastic antibodies in the CSF is confirmatory evidence of a PND of the CNS. Additionally, if an antibody is found but it is not the antibody usually associated with the particular neurologic syndrome of the patient, then other causes for the symptoms should be considered. Similarly, if the detected cancer is not the histological type that typically occurs in association with the antibody, a second neoplasm should be suspected [18, 19].

Establishing the Diagnosis of a PND

In about two thirds of cases, PNDs develop before the diagnosis of cancer [20]. Because early diagnosis and institution of immunomodulatory therapies along with tumor treatment can favorably impact neurologic outcome, it is important that the possibility of a PND be considered when appropriate. In a patient with cancer or in remission, magnetic resonance imaging (MRI) of the involved part of the nervous system is sufficient in most cases to rule out metastasis. In general, MRI has limited diagnostic specificity in PNDs with the exception of limbic encephalitis (Fig. 2). In the early stages of some PNDs, brain 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG-PET) may show hypermetabolic abnormalities in symptomatic brain regions even when the MRI is negative [21]. Sampling of the CSF can reveal evidence of leptomeningeal disease and provides CSF for measurement of paraneoplastic antibodies.

The type of neurologic syndrome can suggest a PND because some syndromes have a paraneoplastic origin more frequently than others, and referral to a neurologist to help define the syndrome can be critical in making the diagnosis. For example, the Lambert-Eaton myasthenic syndrome (LEMS) is likely to be cancer associated in $>50\%$ of patients [22]. In contrast, subacute and chronic mixed sensory–motor neuropathies are much more likely to be a result of nonparaneoplastic causes [23]. The mode of onset can also point to a PND because most PNDs develop acutely or subacutely, with symptoms evolving over weeks or months, in contrast to the chronic and progressive degenerative diseases of middle age and adulthood. Table 3 is a list of neurologic syndromes that are considered classic PNDs and others that may be cancer associated but occur with equal or greater frequency in noncancer settings. The acute or subacute onset of one of the classic syndromes in an adult without a known cancer should lead to an evaluation for an occult tumor, and in a patient with known cancer should lead to screening for possible cancer recurrence [24].

If no clear cause for the neurologic complaints are found and a PND is still suspected, testing for paraneoplastic antibodies can be very useful, and commercial laboratories offer panels of antibody studies based on the predominant symptom type. The specificity of paraneoplastic antibodies for different syndromes or some types of cancer can confirm the PND diagnosis and focus the search for the neoplasm (Tables 1 and 2). If cases are carefully selected based on the syndrome, type of onset, cancer risk, and general clinical suspicion, the likelihood of detecting antibodies is greater [25]. In PNDs of the CNS, antibody titers are usually higher in the CSF than in the serum, so CSF sampling is recommended. This not only offers the best chance to detect antibodies but can provide evidence of inflammatory changes (pleocytosis, elevated protein concentration, and oligoclonal bands) that support the diagnosis of a PND.

Finding an associated neoplasm can support the diagnosis of a PND, but as noted above, in most patients the PND precedes the cancer diagnosis. The tumors more frequently associated with PNDs are those that express neuroendocrine proteins, such as small-cell lung cancer (SCLC) or neuroblastoma, those that affect organs with immunoregulatory functions (thymoma), and those that are derived from cells that produce immunoglobulins (plasma cell dyscrasias, B-cell lymphomas) [26, 27]. Less common, but often associated with highly typical neurologic syndromes, are neoplasms of the ovary or breast, germ-cell tumors of the testis, and teratomas. Because of the common association of breast and gynecological cancers with PNDs, a mammogram and pelvic computed tomography (CT) scan or ultrasound should be carried out in all women with a suspected PND [28]. Whole-body PET scans may detect tumors that escape detection by other standard imaging methods [29, 30]. Men with symptoms of limbic and brainstem encephalitis should be examined for a testicular tumor, and young women should be examined for an ovarian teratoma that may appear as a benign cyst. In both instances, ultrasound and CT of the abdomen and pelvis are useful to identify tumors of the gonads and retroperitoneal space.

For patients with classic PNDs, or those with less classic PNDs but who are positive for paraneoplastic antibodies, in whom a tumor is not found, periodic cancer screening should be considered. In general, a cancer will be identified within the first year of the PND, but there are rare instances when the expected type of tumor was demonstrated several years later [31, 32]. A graphic summarizing the general diagnostic approach is given in Figure 3.

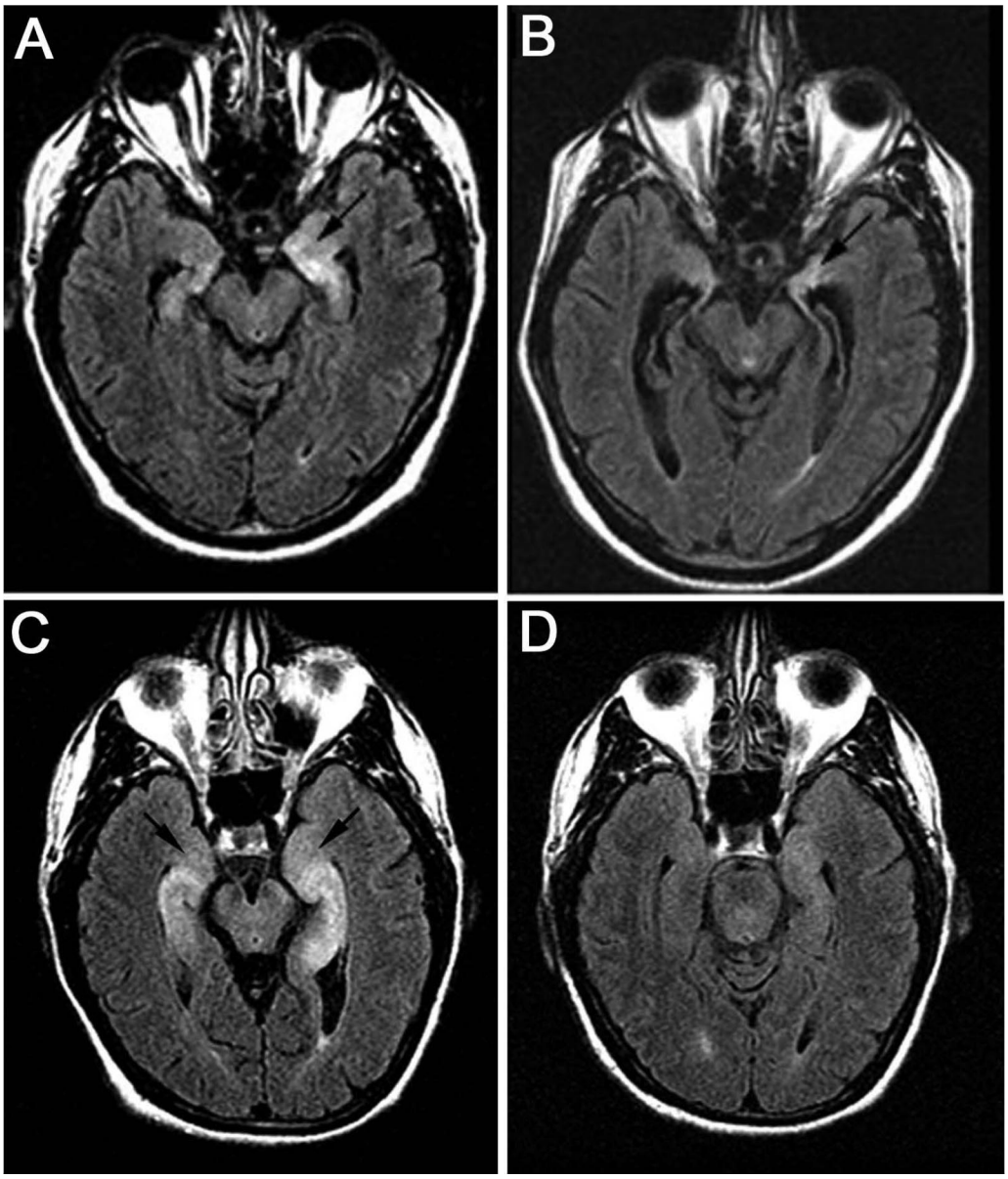

Figure 2. Magnetic resonance imaging (MRI) in limbic encephalitis. Fluid-attenuated inversion recovery (FLAIR) MRI sequences show progressive atrophy of the medial temporal lobes in a patient with paraneoplastic limbic encephalitis associated with antibodies to intracellular neuronal antigens (the MRI images in **(A)** and **(B)** were obtained 16 months apart). The patient's symptoms did not respond to immunotherapy and treatment of the tumor (papillary carcinoma of the thyroid gland). In contrast, the MRI of a patient with limbic encephalitis associated with antibodies to cell surface antigens (voltage-gated potassium channels) shows no development of atrophy (the MRI images in **(C)** and **(D)** were obtained 6 months apart). The patient's symptoms responded to corticosteroids; no tumor was identified. Arrows in **(A)** and **(B)** indicate the same region of the hippocampus. Arrows in **(C)** indicate intense FLAIR changes in both hippocampi.

General Treatment Concepts

The first goal of therapy for PNDs is the identification and treatment of the tumor because this appears to offer the best chance for neurologic stabilization or improvement [19, 33]. This is clearly seen in the neuropathy associated with osteosclerotic myeloma [34]. For those PNDs of the peripheral nervous system in which the antibodies are known to be pathogenic (Table 2), antibody-depleting and immunosuppressant therapies are often quite effective. For disorders of the CNS that are likely antibody mediated (Table 2), the combination of i.v. immunoglobulin (Ig) and plasma exchange may work at early stages of the disease; however, in later stages, when there is high intrathecal synthesis of antibodies, these treatments often fail. In those patients, rituximab and cyclophosphamide are frequently effective [8, 35].

Table 3. Neurologic syndromes and the risk for paraneoplasia

Classic syndromes: usually occur with cancer association	Nonclassic syndromes: may occur with and without cancer association
Encephalomyelitis	Brainstem encephalitis
Limbic encephalitis	Stiff-person syndrome
Cerebellar degeneration (adults)	Necrotizing myelopathy
Opsoclonus-myoclonus	Motor neuron disease
Subacute sensory neuronopathy	Guillain-Barré syndrome
Gastrointestinal paresis or pseudo-obstruction	Subacute and chronic mixed sensory–motor neuropathies
Dermatomyositis (adults)	Neuropathy associated with plasma cell dyscrasias and lymphoma
Lambert-Eaton myasthenic syndrome	Vasculitis of nerve
Cancer- or melanoma-associated retinopathy	Pure autonomic neuropathy
	Acute necrotizing myopathy
	Polymyositis
	Vasculitis of muscle
	Optic neuropathy
	Bilateral diffuse uveal melanocytic proliferation

As noted above, in many PNDs of the CNS T-cell mechanisms are likely important in mediating neuronal destruction. These PNDs tend to be poorly responsive to treatment. In addition to treatment of the tumor, the best chance for neurologic stabilization or improvement is if treatment is given while the PND is still progressing because the neuronal damage may not be complete [36]. In these cases, in addition to corticosteroids, i.v. Ig, or rituximab, more aggressive immunosuppression can be attempted with cyclophosphamide, tacrolimus, or cyclosporine [37, 38].

Concerns that the use of immunosuppression in cancer patients favors tumor growth or that the addition of immunosuppressants to ongoing cancer therapies results in greater toxicity appear unfounded [39]. Experience with PNDs and other disorders, such as lymphoma, demonstrates that corticosteroids, i.v. Ig, plasma exchange, and rituximab are well tolerated by most patients who are also receiving chemotherapy [37].

Clinical Characteristics

Encephalomyelitis

Patients with paraneoplastic encephalomyelitis (PEM) develop dysfunction at multiple levels of the nervous system [19, 40]. Symptoms include limbic or brainstem encephalitis, cerebellar degeneration, myelitis, and/or sensory and autonomic neuropathies [40–42]. Although PEM can be associated with almost any type of cancer, the majority of patients have lung carcinoma, particularly SCLC. Many patients, and in particular those who have an associated sensory neuronopathy and SCLC, have anti-Hu antibodies or, less commonly, anti-CV2/collapsin response-mediator protein (CRMP)-5 antibodies [43–45]. In general, PEM is poorly responsive to treatment, although symptom stabilization or improvement may occur with prompt tumor therapy.

Cerebellar Degeneration

The acute or subacute onset of rapidly progressive cerebellar dysfunction in an adult should lead to the suspicion of a PND because noninflammatory degenerative cerebellar disorders evolve over months to years. Symptoms include dizziness, oscillopsia, double vision, dysarthria, and nausea and vomiting that usually progress within days or even hours to affect all limbs and trunk, resulting in severe disability. The examination shows limb and gait ataxia and, frequently, downbeating nystagmus.

The most commonly associated tumors are SCLC, cancers of the breast and ovary, and Hodgkin's lymphoma [46]. In patients with SCLC, the development of paraneoplastic cerebellar degeneration (PCD) may be the presenting symptoms of PEM, and in these cases anti-Hu or anti-CV2/CRMP-5 antibodies are usually identified. Anti-Yo and, less frequently, anti-Ri antibodies are found in women with breast or gynecologic cancers, although there are rare cases of men with anti-Yo antibodies and a variety of associated tumors [47, 48]. In patients with Hodgkin's disease, PCD in association with anti-Tr antibodies may develop before or after the lymphoma diagnosis, or may herald lymphoma recurrence [49].

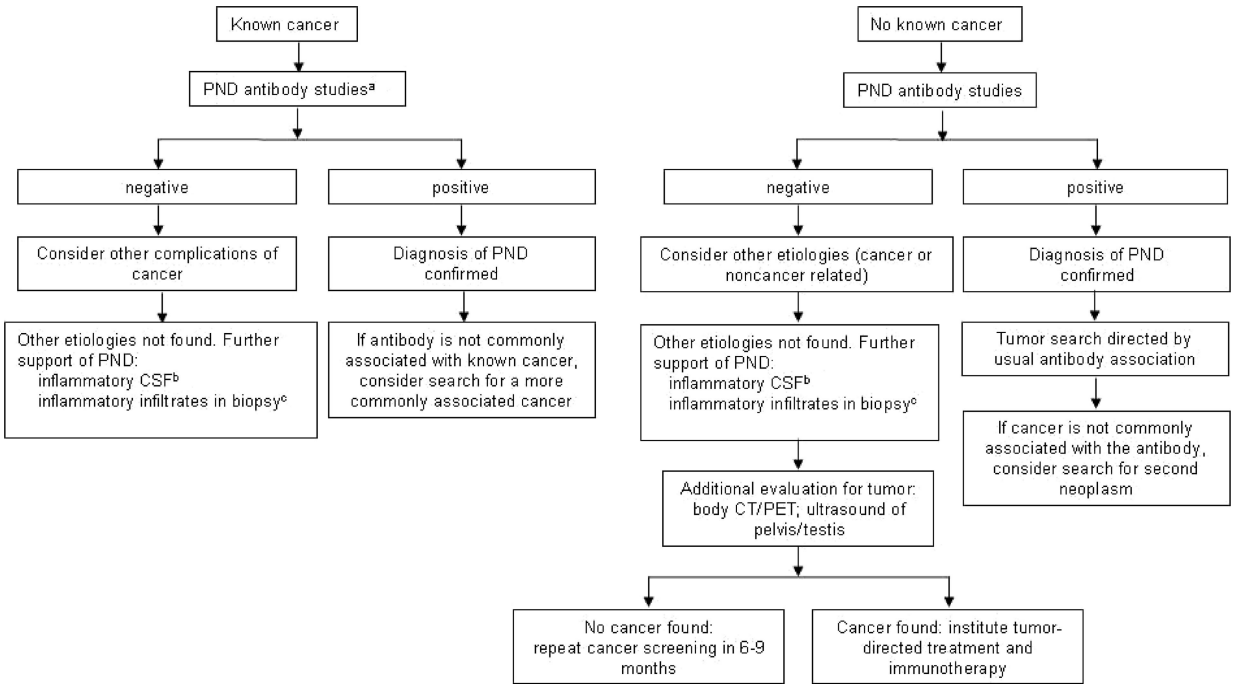

Figure 3. Diagnostic approach in a patient with a suspected paraneoplastic neurologic disorder.
[a]PND antibody studies refer to well-characterized paraneoplastic antibodies (see Table 1).
[b]CSF inflammatory changes include lymphocytic pleocytosis, elevated IgG index, and oligoclonal bands with or without elevated protein concentration.
[c]Biopsy should be directed to symptomatic area of the nervous system (clinical or by MRI).
Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PET, position emission tomography; PND, paraneoplastic neurologic disorder.
Adapted from Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008;7:327–340, with permission from Elsevier.

Treatment of PCD is often unsuccessful, although there are reports of improvement with tumor treatment and immunotherapy if patients are treated while symptoms are still progressing [50, 51].

Limbic and Brainstem Encephalitis

Limbic encephalitis is characterized by short-term memory deficits with relative preservation of cognitive functions and often partial complex seizures [52, 53]. Brainstem encephalitis is characterized by cranial nerve abnormalities leading to eye movement disorders, dysarthria, and dysphagia, among others. Limbic encephalitis is one of the few PNDs for which neuroimaging can help to establish the diagnosis [54]. Typical MRI findings include predominant unilateral or bilateral abnormalities in the hippocampus, best seen on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images [53, 55, 56]. These findings may be subtle, and the radiologist should be made aware of the possible diagnosis of limbic encephalitis. Contrast enhancement is rare, but its presence can lead to the suspicion of a metastasis [57]. When limbic encephalitis is mediated by cytotoxic T-cell mechanisms (usually in association with antibodies to intracellular antigens—Hu, Ma2, or CV2/CRMP), the response to treatment is limited and the MRI often shows progressive atrophy of the medial temporal lobes. This is in contrast to several types of reversible limbic encephalitides that are suspected to be mediated by antibodies against cell surface antigens (discussed below, Fig. 2). The presence of inflammatory changes in the CSF supports a PND diagnosis over that of a tumor.

The most commonly associated cancers are SCLC, testicular germ-cell tumors, teratoma (usually of the ovary), thymoma, and Hodgkin's lymphoma [53]. A variety of antibodies may be found, and titers in the CSF are often substantially higher than in the serum. Patients with anti-Hu antibodies and SCLC have limbic encephalitis as part of PEM [40]. Less commonly, these patients have anti-CV2/CRMP antibodies [58]. Men aged <45 years are likely to have antibodies to Ma proteins (mainly Ma2) and a testicular germ-cell tumor [10]. In addition to limbic and brainstem encephalitis, patients with antibodies to Ma proteins often have dysfunction of the hypothalamus and associated regions, leading to hypersomnia, hypothalamic hormonal deficits, cataplexy, and narcolepsy [57, 59]. In some pa-

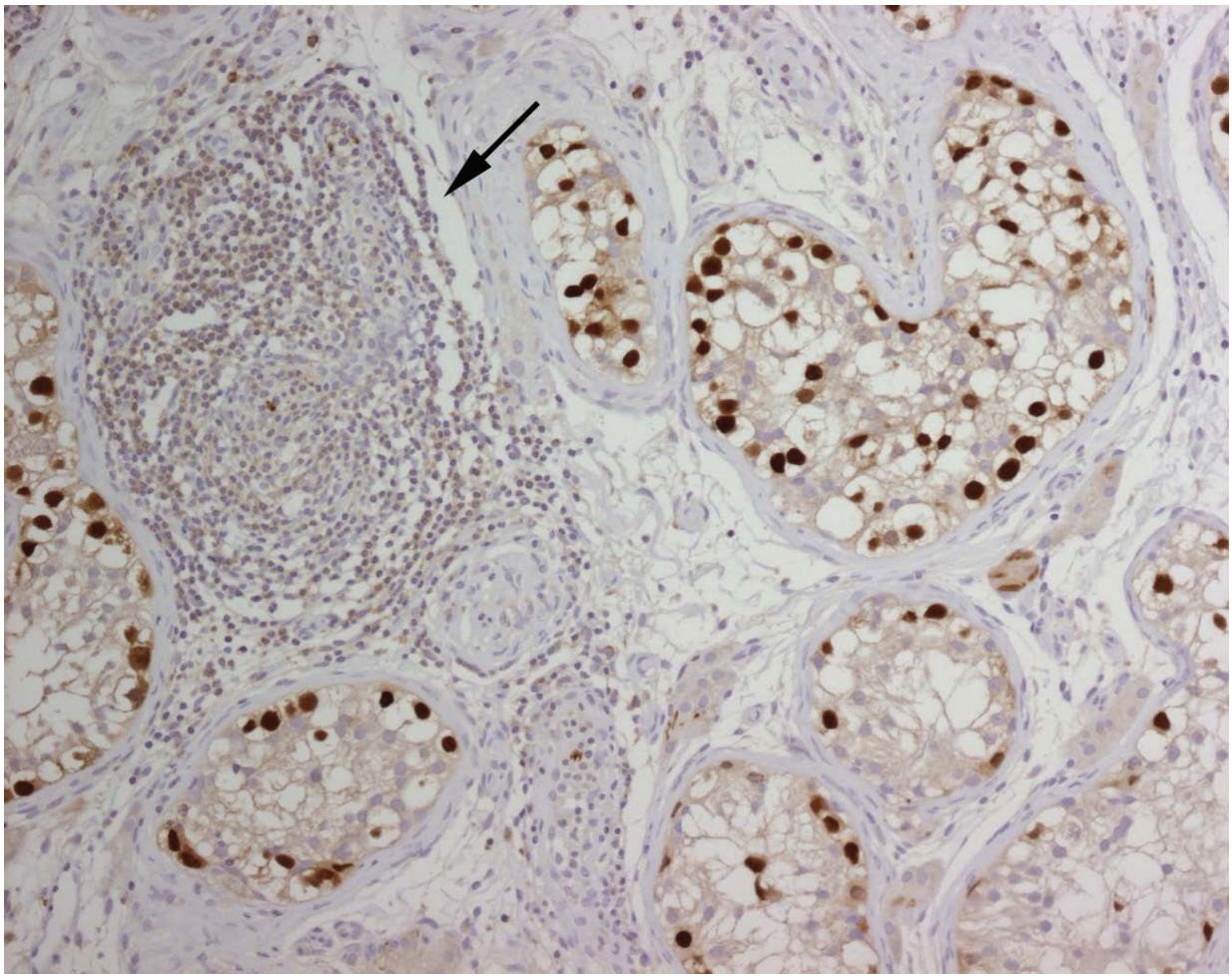

Figure 4. Intratubular germ-cell neoplasm of the testis in a patient with paraneoplastic anti-Ma2 encephalitis. Section of a microscopic germ-cell neoplasm of the testis (carcinoma in situ) from a patient with anti-Ma2–associated encephalitis. The neoplastic cells (dark-brown nuclei) are demonstrated with an antibody against Oct4 (a specific neoplastic marker). The arrow indicates the presence of an inflammatory infiltrate.

tients, the combination of thalamic and brainstem dysfunction presents with severe hypokinesis, reduction of speech, and vertical gaze paresis, and may be misdiagnosed as Whipple's disease [60, 61]. Prompt recognition of anti-Ma2 encephalitis is important because about 35% of patients respond to tumor removal and immunotherapy [62]. The associated testicular tumor is often difficult to demonstrate and frequently is suggested only by the demonstration of testicular microcalcifications (Fig. 4) [63].

Encephalitides with Antibodies to Cell Surface or Synaptic Proteins

An emerging group of encephalitides associates with antibodies to cell surface or synaptic proteins, including proteins that coprecipitate with voltage-gated potassium channels (VGKCs), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, the γ-aminobutyric acid type B [GABA(B)] receptor, and the N-methyl-D-aspartate (NMDA) receptor [7, 64–66]. For these disorders, there is strong evidence that the antibodies are pathogenic, and removal of the antibodies and antigenic source (tumor if found) often associates with clinical improvement. As with limbic encephalitis, the diagnosis can be assisted by MRI findings of increased FLAIR signal involving the temporal lobes.

Patients with antibodies to proteins that associate with VGKCs develop typical features of limbic encephalitis often in association with hyponatremia and sleep and autonomic dysfunction [66, 67]. A lower number of patients develop neuromyotonia (or peripheral nerve hyperexcitability). Only about 20% of these cases are paraneoplastic, and the commonly associated tumors are SCLC and thymoma [66, 68, 69].

Patients with AMPA receptor antibodies are usually middle- aged women who develop acute limbic dysfunction or, less frequently, prominent psychiatric symptoms [7].

About 70% of patients have an underlying tumor in the lung, breast, or thymus. The neurological disorder responds to tumor treatment and immunotherapy, but has a tendency to neurological relapses that respond to immunotherapy; relapses are not necessarily associated with tumor recurrence.

The encephalitis associated with GABA(B) receptor antibodies usually presents with limbic encephalitis and seizures [64]. About 50% of the patients have SCLC or a neuroendocrine tumor of the lung. Neurological symptoms often respond to immunotherapy and treatment of the tumor, if found. Patients frequently have additional antibodies to glutamic acid decarboxylase (GAD), which is of unclear significance. Other antibodies to non-neuronal proteins are often found in these patients as well as in patients with AMPA receptor antibodies, indicating a tendency to autoimmunity.

Anti-NMDA receptor encephalitis is most common in young women and children, but men and older patients of both sexes can be affected [65]. Over half of the patients have an associated tumor, most commonly a mature or immature teratoma of the ovary that can be mistaken for a benign cyst. The disorder has a characteristic pattern of symptom progression that includes prodromal symptoms resembling a viral process followed in a few days by the onset of severe psychiatric symptoms, memory loss, seizures, decreased consciousness, abnormal movements (orofacial, limb, and trunk dyskinesias; dystonic postures), autonomic instability, and frequent hypoventilation. The disorder is often misdiagnosed as viral or idiopathic encephalitis, neuroleptic malignant syndrome, or encephalitis lethargica, and frequently patients are initially evaluated by a psychiatrist with the suspicion of drug abuse or an acute psychotic break [70, 71]. The detection of an ovarian teratoma is age dependent; approximately 50% of female patients aged >18 years have uni- or bilateral ovarian teratomas, whereas $<9\%$ of girls aged <14 years have a teratoma [8, 72]. In male patients, the detection of a tumor is rare.

The importance of recognizing these disorders promptly is that, despite the severity of the symptoms, patients usually respond to treatment of the tumor, if found, and immunotherapies. The response to treatment of patients with anti-NMDA receptor encephalitis is usually slow, often requiring at least 2–3 months of hospitalization followed by physical and behavioral rehabilitation [8, 73, 74].

Opsoclonus-Myoclonus

This disorder is also known as dancing eyes and feet syndrome because of the associated rapid and irregular eye movements and quick involuntary jerking (myoclonus) of the head, trunk, or extremities. In adults, symptoms range from opsoclonus with mild truncal ataxia to a severe syndrome characterized by opsoclonus, myoclonus, ataxia, and encephalopathy that can lead to stupor and death. In children, the onset of gait disturbance and falling can lead to an initial diagnosis of viral cerebellitis.

The majority of adults with paraneoplastic opsoclonus-myoclonus have an underlying SCLC, although other cancers have been reported [75]. Most patients do not have well-characterized antibodies except for a small subgroup of patients, usually women with breast or gynecologic cancers, who develop opsoclonus-myoclonus with ataxia in association with anti-Ri antibodies [76].

In children, opsoclonus-myoclonus is a well-known complication of neuroblastoma, and the neurological symptoms precede the tumor diagnosis in 50% of patients. Children with neuroblastoma and opsoclonus have a better tumor prognosis than those without paraneoplastic symptoms. The syndrome often responds to treatment of the tumor along with prednisone, adrenocorticotrophic hormone, i.v. Ig, or rituximab [77]. However, most children are left with behavioral abnormalities, language and psychomotor deficits, and sleep disturbances; the latter may respond to trazodone [78, 79]. In adults, paraneoplastic opsoclonus-myoclonus may partially respond to immunosuppression and i.v. Ig, but tumor control is required to obtain a complete or sustained neurological response [75].

Subacute Sensory Neuronopathy

Patients with this disorder develop progressive loss of all modalities of sensation that is often initially asymmetric and may affect cranial nerves [40, 80]. The disorder results from an inflammatory- or autoimmune-mediated destruction of the dorsal root ganglia. This is in contrast to the distal bilaterally symmetric symptoms of many toxic or metabolic neuropathies that preferentially affect some sensory modalities over others [80].

A number of cancers have been associated with subacute sensory neuronopathy (SSN), but the most common is SCLC. Many of these patients have SSN in association with PEM and anti-Hu antibodies, although these antibodies are rarely found if the associated tumor is not SCLC [19].

The neurological symptoms of patients with SSN, SCLC, and anti-Hu antibodies whose tumors respond to therapy are more likely to stabilize or improve than those of patients with untreated tumors or tumors that do not respond to therapy [19, 46]. In some patients, prompt treatment with corticosteroids may partially improve the sensory deficits [37].

Subacute and Chronic Peripheral Neuropathies

The development of peripheral nerve dysfunction in cancer patients is common, and in most patients is not paraneoplas-

tic. Nutritional deficits and hepatic or renal failure are often involved and should be considered, especially in patients with advanced disease or significant weight loss. Leptomeningeal metastases should be suspected if the findings are multifocal or asymmetric, or if cranial nerves are also involved. Treatment with neurotoxic chemotherapies is associated with distal and symmetric sensory or sensorimotor deficits usually affecting the legs before the arms, whereas mononeuropathies or plexopathies are concerning for metastatic invasion of the nerves or plexuses. Neuroimaging with MRI, CSF analyses, electrophysiological studies, and, less frequently, nerve biopsy often clarify the etiology. The diagnosis of a paraneoplastic neuropathy is therefore one of exclusion. Antibody studies are of limited help because most cases of paraneoplastic neuropathy do not have associated antibodies [81]. One exception is some patients with lung cancer and thymoma, who may harbor CV2/CRMP-5 antibodies. Of note, patients with SSN caused by dorsal root ganglia involvement may also have a peripheral neuropathy; these patients have anti-Hu antibodies.

For patients with solid tumors, most commonly of the lung or breast, a paraneoplastic sensorimotor neuropathy can develop before or after the diagnosis of cancer [82]. The onset may be subacute or acute, and the course is usually progressive. A relapsing and remitting course suggests chronic inflammatory demyelinating polyneuropathy (CIDP). Treatment of the tumor may be associated with improvement, and for patients with electrophysiological signs of demyelination, steroids and i.v. Ig may be useful.

Patients with multiple myeloma may develop a sensorimotor neuropathy similar to that seen in patients with other advanced cancers [83]. When associated with amyloidosis, there is also autonomic dysfunction and lancinating and burning dysesthesias. In both cases, the course of the neuropathy may become independent of the myeloma. Osteosclerotic myeloma is often associated with a symmetrical, distal sensorimotor neuropathy with predominant motor symptoms that resemble CIDP, or with additional symptoms indicative of POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, and *s*kin changes) [84, 85]. Patients often have one or just a few osteosclerotic lesions that tend to involve the spine and proximal long bones. Irradiation of the lesions may result in improvement of the neuropathy, especially when combined with chemotherapy and surgery [34]. Some patients with POEMS syndrome and a rapidly progressive neuropathy improved after peripheral blood stem cell transplant [86].

Polyneuropathy in association with Waldenström's macroglobulinemia often presents with discomfort and distal symmetric sensory loss in the legs. Vibration and pin sensation are most affected. In some patients, the neuropathy is a result of the deposition of serum IgM in peripheral nerves, sometimes with antibody activity against myelin-associated glycoprotein and gangliosides [87, 88]. The neuropathy may respond to treatment directed at Waldenström's macroglobulinemia. There is a case report of a patient who had significant worsening of neuropathy in temporal relationship to treatment with prednisone, fludarabine, and rituximab, possibly as a result of an increase in IgM levels [89].

A variety of neuropathic syndromes associates with Castleman's disease (angiofollicular lymph node hyperplasia), including painful sensorimotor, chronic relapsing sensorimotor, and predominantly motor neuropathies [90, 91]. Treatment is focused on the tumor, although neurological improvement has been reported with plasma exchange, corticosteroids, and cyclophosphamide [90, 92].

An acute paraneoplastic inflammatory demyelinating polyneuropathy identical to Guillain-Barré syndrome (GBS) occurs in association with a variety of cancers, especially Hodgkin's lymphoma, and in patients receiving autologous and allogeneic bone marrow transplantation for cancer treatment [93, 94]. The syndrome is characterized by loss of deep tendon reflexes and an ascending, predominantly motor neuropathy that can involve cranial nerves and those innervating the diaphragm, leading to depressed respiratory function. Typical CSF findings are elevated proteins without increased cell counts. In some patients, GBS may be the first manifestation of tumor recurrence. Treatment consists of plasma exchange and i.v. Ig. There is some evidence suggesting that patients with GBS and cancer have a worse neurologic outcome than those without cancer [95].

Paraneoplastic Vasculitis

Systemic paraneoplastic vasculitis of the small vessels of the skin can be seen with lymphomas and leukemias [96, 97]. In contrast, paraneoplastic microvasculitis of the muscle and nerve without systemic vasculitis is more often reported in association with solid tumors, and should be considered when patients, especially older individuals, develop symptoms of symmetric or asymmetric painful sensorimotor neuropathy often accompanied by proximal muscle weakness [98]. No specific antibodies have been identified in any of the paraneoplastic vasculitidies, although anti-Hu antibodies are found in some patients with SCLC. The disorder often responds to corticosteroids and cyclophosphamide.

LEMS

This is a classic paraneoplastic syndrome, and its presence should always raise a strong suspicion of an associated can-

cer, in particular SCLC. Patients usually complain of generalized fatigue, dry mouth, and difficulties walking because of leg weakness [22]. Some patients report increased strength after a period of activity. In addition to dry mouth, at least half of the patients have autonomic dysfunction, such as erectile dysfunction, constipation, and orthostatic hypotension [99]. Respiratory muscle weakness is rare but can lead to respiratory failure. In most patients, LEMS develops before the tumor is diagnosed. The development of LEMS after cancer remission should lead to evaluation for tumor recurrence.

Patients with LEMS have serum antibodies against the P/Q type voltage-gated calcium channels expressed in the cancer and neuromuscular junction [100]. The antibodies interfere with the release of acetylcholine, resulting in failure of neuromuscular transmission. LEMS can develop in association with PEM, in which case patients often have anti-Hu antibodies [101].

The diagnosis is based on electrophysiological studies and supported by antibody studies. Most patients with cancer improve with combined treatment of their cancer and therapy for LEMS. Plasma exchange and i.v. Ig often result in improvement of strength within days or weeks, but benefits are transient. Some patients require long-term immunosuppression with prednisone or azathioprine. The drug 3,4-diaminopyridine increases the release of acetylcholine and results in moderate to marked neurological improvement in most patients [102]. It was recently designated as an orphan drug by the U.S. Food and Drug Administration and this should facilitate its use.

Stiff-Person Syndrome

Stiff-person syndrome is characterized by progressive muscle stiffness and rigidity that develops over months and is most prominent in the back muscles and legs. Additional symptoms include muscle aches and painful spasms that are triggered by a variety of stimuli. Stiff-person syndrome is more often nonparaneoplastic (about 80% of cases) and occurs in association with antibodies against GAD. This type of autoimmunity also associates with cerebellar ataxia, diabetes mellitus, and other endocrine deficits [103]. When stiff-person syndrome is paraneoplastic, the tumors most commonly involved are breast cancer, SCLC, thymoma, and Hodgkin's lymphoma. A subset of patients, mostly with breast cancer and SCLC, develops antibodies to amphiphysin, although these can also occur in patients with other paraneoplastic syndromes, such as encephalitis [104, 105]. The treatment strategy is based on treating the tumor, immunotherapy (corticosteroids, i.v. Ig), and the use of drugs that enhance GABAergic transmission (diazepam, baclofen).

Paraneoplastic Visual Syndromes

Paraneoplastic visual syndromes are rare, and when patients with cancer develop visual complaints, the more important considerations are metastatic infiltration of the optic nerves by leptomeningeal disease, choroid metastases, and toxic effects of therapy. Cancer-associated retinopathy (CAR) can occur with any solid tumor but is more commonly reported in association with SCLC [106, 107]. Melanoma-associated retinopathy (MAR) affects patients with metastatic cutaneous melanoma, often months or years after the initial diagnosis [108]. The diagnosis of CAR and MAR is based on specific abnormalities seen on the electroretinogram and can be supported by antibody studies. Antibodies to recoverin [109], a calcium-binding photoreceptor protein, are most common in CAR; however, >20 other antibodies targeting other retinal antigens have been described [110–112]. Patients with MAR typically have antibodies that react with the bipolar cells of the retina; several candidate autoantigens (e.g., arrestin and transducin) have been reported [113].

Treatment of the associated tumor may be associated with stabilization or improvement of vision. In general, response to corticosteroids is poor. There are case reports of improvement with i.v. Ig, plasmapheresis, or alemtuzumab [114].

Paraneoplastic optic neuropathy presents with subacute, painless, bilateral visual loss. The examination may show optic disc swelling or atrophy that may associate with vitritis [115]. In some cases, antibodies to CV2/CRMP-5 have been reported [116]. The neurologic and visual prognosis seems to be dependent on how well patients respond to treatment of their underlying malignancy. Systemic corticosteroids and intravitreal corticosteroids have been reported to be effective in decreasing vitreal inflammatory infiltrates and stabilizing or improving vision [115, 117].

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is characterized by diffuse bilateral proliferation of melanocytes in the uveal tract, leading to bilateral visual loss [118]. It has been described in women with carcinoma of the reproductive tract and in men, most commonly with carcinomas of the lung and pancreas. In most cases, the BDUMP precedes the cancer diagnosis [119, 120]. It is not clear if the uveal melanocytes are benign or have metastatic potential, and treatments have not been systematically evaluated. Corticosteroids do not appear to impact the process, and several cases in which the choroidal lesions were irradiated had worsening of vision.

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